



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b>  <b>A61K 31/00</b>	<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 00/23056</b>  <b>(43) International Publication Date:</b> 27 April 2000 (27.04.00)
<b>(21) International Application Number:</b> PCT/CA99/00977  <b>(22) International Filing Date:</b> 20 October 1999 (20.10.99)  <b>(30) Priority Data:</b> 2,251,255                      20 October 1998 (20.10.98)                      CA  <b>(71) Applicant (for all designated States except US):</b> MCGILL UNIVERSITY [CA/CA]; 3550 University Street, Montreal, Quebec H3A 2A7 (CA).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> KARPATI, George [CA/CA]; 5726 Chemin Queen Mary, Hampstead, Quebec H3X 1X8 (CA). MOLNAR, Maria, Jutka [HU/CA]; 3550 University Street, Montreal, Quebec H3A 2A7 (CA).  <b>(74) Agents:</b> DUBUC, Jean, H. et al.; Goudreau Gage Dubuc & Martineau Walker, The Stock Exchange Tower, Suite 3400, 800 Place Victoria, P.O. Box 242, Montreal, Quebec H4Z 1E9 (CA).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> THE USE OF DOPAMINERGIC AGENTS IN THE MANAGEMENT OF SEXUAL DYSFUNCTION  <b>(57) Abstract</b>  This invention relates to a new use of dopaminergic agonists for improving sexual function, particularly erectile function. Preferred agonists are pramipexol and ropirinol which present much less side effects than agonists of previous generations. Pramipexol has been further used successfully in combination with sildenafil. A new pharmaceutical composition comprising both a vasodilating agent such as sildenafil and a dopaminergic agonist is described and claimed.		

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**TITLE OF THE INVENTION**

The use of dopaminergic agents in the management of sexual dysfunction.

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**FIELD OF THE INVENTION**

The invention relates to the use of dopaminergic agents, namely pramipexol, for improving or obtaining sexual function, particularly in males.

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**BACKGROUND OF THE INVENTION**

The effects of dopamine agonists on sexual function are known to the practitioners. In most cases, a decrease of the libido is reported when dopamine agonists are administered alone, although some mild and inconsistent enhancement of sexual function has been noted during the treatment of Parkinson's disease with agonists such as amantadine, parlodel, bromocriptine and bupropion. Paradoxically, it is also known that dopaminergic agents enhance libido when co-administered with antidepressives, which themselves decrease libido.

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Amantadine, parlodel, bromocriptine and bupropion are examples of dopaminergic agents having a weak activity with severe side effects. Pramipexol (1 to 5 mg / daily dose divided in 3 doses) and ropirinol ( 3 to 24 mg / daily dose in 2 or 3 subdivided doses) are two promising agonists for the treatment of Parkinson's disease, these drugs having much less undesirable side effects than other dopaminergic agents.

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Ropirinol is a selective D<sub>2</sub>- agonist while pramipexol is a selective D<sub>3</sub>- agonist with a D<sub>2</sub>- presynaptic activity. It is believed that dopaminergic agonists having an effect mediated at least by one or both of these two types of receptors would be useful in the present invention. It is also possible that any  
5 dopaminergic agonist will fulfil the promise of this invention, although those having less side effects are preferred.

A rare incidence of decreased libido or impotence is reported for pramipexol  
10 and ropirinol when administered to Parkinson's patients not concomitantly treated with levodopa. To the inventors' surprise, patients treated with pramipexol has noticed, on the contrary, an increase of the libido and penile rigidity (that should not be confused with priapism which is an undesirable, uncontrollable  
15 and painful penile rigidity). It was further observed that penile rigidity can be enhanced by the *ad hoc* administration of sildenafil which further improved capacity for full and sustained penetration during sexual intercourse.

## 20 STATEMENT OF THE INVENTION

These observations open a new avenue for potential uses of dopaminergic agonists such as pramipexol and pharmacologically equivalent drugs, namely ropirinol, alone or in combination with vasodilating drugs maintaining a high  
25 nitric oxide level, such as sildenafil.

It is worthwhile noting that about 35% of the patients do not respond to sildenafil. Those patients may respond to a combination of sildenafil and pramipexol.

It is therefore an object of the present to provide a new use of a dopaminergic agonist in the making of a medication to improve sexual function in a subject. These agonists preferably have an effect mediated by dopamine receptors of type 2, or type 3, or both. Examples of preferred agonists are ropirinol and  
5 pramipexol. In a most preferred embodiment the agonist is pramipexol and it has been tested at a dose of 0.125 to 0.250 mg. The agonist is used alone or combined to an effective vasodilating amount of an agent capable of maintaining a high nitric oxide level. Such an agent is sildenafil. Doses of 50 to 100 mg have been tried with success. This invention is particularly useful  
10 to improve erectile function.

It is another object of this invention to provide a pharmaceutical composition comprising an effective amount of dopaminergic agonist for improving sexual function in combination with a vasodilating amount of an agent capable of  
15 maintaining a high nitric oxide level, and an acceptable pharmaceutically acceptable carrier. The agonist preferably has an effect mediated by dopamine receptors of type 2, or type 3, or both. Examples of preferred agonists are ropirinol and pramipexol. In a most preferred embodiment, the agonist is pramipexol, and it has been tested at a dose of 0.125 to 0.250 mg.  
20 The agent is sildenafil. It has been tested at a dose of 50 to 100 mg.

#### **DESCRIPTION OF THE INVENTION**

Without being bound to any theory, the inventors have made a  
25 comprehensive review of the mechanisms involved in sexual function and tried to draw a *rationale* for the effect of dopaminergic agonists such as pramipexol on sexual function.

For practical reasons, the discussion is directed to male sexual function. Measurable parameters and visual observations can be more objectively obtained in male subjects for obvious reasons. It is however not excluded that women may benefit from the present invention.

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#### PHYSIOLOGICAL AND PHARMACOLOGICAL BACKGROUND OF THE MALE SEXUAL REFLEXES

There are 4 principal male sexual reflexes: libido, erection, ejaculation and orgasm. The anatomical substrate, the neural pathways and the  
10 neurochemical transmitter profile for each of these reflexes are understood to a variable degree.

The libido, or sexual drive is primarily determined by male hormones via their action on central nervous system structures in the hypothalamus and limbic  
15 system.

The erection reflex has a segmental and suprasegmental component. The segmental or spinal reflex is influenced by both sympathetic and parasympathetic nerves. The sympathetic nerves originate from the T11-L2  
20 cord levels and reach the target tissues via the hypogastric nerves, pelvic plexus, cavernous nerves and pudendal nerves as postganglionic fibers. The parasympathetic innervation originates from the S2-4 spinal segments and reach the target tissue as nervi erigentes and the pelvic plexus mixed with sympathetic nerves. Descending suprasegmental tracts both facilitate and  
25 inhibit the erection reflex. These pathways originate in the hypothalamus and limbic system, the hypothalamic medial preoptic area being the principal integrating center. The tracts descend through the median forebrain bundle, ventrolateral pons and medulla and the lateral columns of the spinal cord.

The neurochemical transmitters for the sympathetic nerves is norepinephrine while acetylcholine is for the parasympathetic nerves. **The facilitatory central pathways are dopaminergic.** The erection reflex is facilitated at the segmental level by parasympathetic fibers and inhibited by sympathetic nerves.

5 The erection reflex can be initiated by mechanical stimulation of the peripheral erogenic zones which sets up a primary spinal reflex or by psychogenic stimuli which, through the central facilitatory pathways, sets up a secondary spinal reflex. Synergistic action of both systems are the most efficient. The facilitatory neural impulses for the erection reflex causes  
10 massive vasodilation of the penile arteries, maximum filling of the expandable caverns of the corpora cavernosa, and passive compression of the effluent veins. As a result, a marked increase of the penile tumescence occurs. The marked penile arterial vasodilation, which is the ultimate final effector mechanism bringing about erection, is predicated upon relaxation of the  
15 arterial smooth muscle. This, in turn, is activated by the rapid synthesis of NO and possibly other vasoactive peptides. NO synthesis is facilitated by cyclic GMP which is degraded by a specific phosphodiesterase. Therefore, the erection reflex can be stimulated by inhibiting this enzyme which would maintain a high NO level. Sildenafil (Viagra™) is such a compound.

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In summary on the basis of the above facts, the erection reflex can be stimulated at the level of penile smooth muscle (dilation), or stimulation of the parasympathic nerves and/or inhibiting the sympathetic nerves, or by stimulating the central dopaminergic system or perhaps a judicial  
25 combination of more than one factors.

The neural pathways that mediate the ejaculation reflex is similar to those of the erection reflex but the trigger signal is mainly a sympathomimetic one.

This indicates the fine tuning of the plasticity and the dynamic equilibrium that must operate to ensure effective sexual function. The ejaculation reflex activates smooth muscles in the seminal vesicles and prostate and mediated by fibers in the pudendal nerve. This action expels the semen and usually is associated with orgasm. While the ejaculation reflex usually occurs while the erection is still in full force, ejaculation and orgasm may still occur without significant erection.

Orgasm is a complex sensory experience mainly localized to the erogenic zones and require the integrity of somatic sensory afferent fibers in the pudendal nerve. Orgasm is also associated with complex autonomic phenomena (breathing, pulse, blood pressure, etc.) and psychological experience all of which require the integrity of still undefined peripheral and central neural pathways.

#### RATIONALE FOR USING DOPAMINERGIC AGENTS FOR IMPROVING MALE SEXUAL FUNCTIONS

From the foregoing discussions it becomes clear that abnormal or defective sexual reflexes may arise from pathological alterations of the nerves and neuronal centers that mediate and control these reflexes. Abnormalities of the relevant sympathetic or parasympathetic or somatosensory afferent nerves at the periphery can be involved in a great variety of diseases such as peripheral neuropathies (i.e. diabetes) or myelopathies (i.e. trauma, multiple sclerosis, etc.). Another common cause of erectile dysfunction is vascular insufficiency with impaired blood flow to the penile arteries or defective smooth muscle dilatation in response to the parasympathetic nerve signal. These peripheral causes of erectile dysfunction can be treated by vasodilatory agents or drugs that increase NO level of arterial smooth



muscles (i.e. Sildenafil). However in a substantial number of cases impaired sexual reflexes and erectile dysfunction can be caused mainly by a defect in the facilitatory central pathways for the segmental reflexes. **These pathways are dopaminergic.** Hypoactive suprasegmental facilitation of the sexual reflexes may occur in psychiatric diseases (i.e. depression) or simply because of anxiety and stress or due to undetermined causes. The administration of vasodilatory treatment modalities for such cases will only be partially useful. However, **dopaminergic drugs can be expected to restore the facilitation of the various sexual reflexes, particularly those subserving erection.** Such an approach may also be effective to supplement peripheral vasodilatory treatment when the main dysfunction is peripheral. Some mild and inconsistent enhancement of sexual function has, indeed, been noted during the administration of dopamine agonists such as amantadine, pramipexol, bromocriptine and bupropion. However these were relatively weak dopaminergic agents with severe side effects. With the advent of new agonists such as pramipexol, the situation has dramatically changed.

#### PRELIMINARY CLINICAL OBSERVATIONS

In 1997, pramipexol hydrochloride or PH (Mirapex) has been introduced into the treatment of Parkinson's disease either to boost the action of levodopa or as a first-line medication. As noted later PH is a potent ligand for all classes of striatal dopamine receptors and produces strong dopaminergic stimulation without significant major side effects. This has been a big improvement over previously available direct dopaminergic agents. In our practice we have encountered 5 idiopathic Parkinson's patients in stages 1-2 of the disease, who were taking therapeutic doses (about 1 mg tid) of Mirapex. These patients noted marked improvement of their bradykinesia

and rigidity of limbs, but in addition they noted 2 additional features that could not by any means be attributed to the motor effects of Mirapex. This included a conspicuous sustained increase of the caliber and length of the penile shaft as well as a sustained increase of tumescence. However, this did not reach the state of priapism and there was no penile discomfort at all. In addition, the 5 male patients observed that upon normal natural stimulation of the penis during sexual encounters, a much firmer and more sustained erection could be attained and there was a facilitation of the ejaculation and the intensity of orgasm. In 2 patients, the additional use of Viagra™ (one single dose of 50-100 mg) further improved these functions and there were no harmful interactions between PH and Viagra™. From these observations and from the above discussed central neurotransmitter pharmacology, there is a real potential of using PH to correct or improve erectile dysfunction not only in patients with central and/or peripheral erectile dysfunction, but also in patients who suffer penile atrophy (affecting the corpora cavernosa) after prostatectomy. The dosage of Viagra™ in a combined medication may be reduced, if still effective when used with a dopaminergic agonist.

Six normal male subjects, young and middle aged persons (24 to 60 years old) were given a single *per os* dose of 0.125 - 0.250 mg of PH (MIRAPEX™). They reported a substantially improved erectile function (quality and sustainability). The effect was manifest a few hours after ingestion, and lasted for a day or so. No significant side effects were noted.

This is a clear demonstration that subjects suffering of erectile dysfunction but otherwise healthy will respond to dopaminergic agents, that have been used in the past for treating Parkinson disease.

### DESCRIPTION OF SALIENT FEATURES OF PRAMIPEXOL HYDROCHLORIDE

Pramipexol is an agonist of all classes of central and peripheral dopamine receptors. It is excreted in the urine. The drug is indicated to treat early and late Parkinson's disease alone or in combination with Levodopa. The average daily dose of 1 mg tid po must be built up gradually over a period of weeks. Side effects, usually with full dose, include orthostatic hypotension, hallucination, dyskinesias, headache, constipation and somnolence. Side effects are mild and rare. Serious drug interaction may occur with agents that tend to cause hypotension. Therefore, its combined use with Sildenafil hydrochloride should be envisaged cautiously. At least the same careful approach as the one used to prescribe Sildenafil to patients should be undertaken before considering any combined medication which include Sildenafil.

### OBJECTS OF THE PRESENT INVENTION

Based on the above observations, the present invention provide a therapeutic usefulness of pramipexol for male sexual dysfunction in the following situations:

- a) A single-time use for obtaining or improving erection otherwise not possible, without or with Sildenafil, in patients with central or peripheral neurogenic erectile dysfunction;
- b) A chronic use of a dose for the purpose of obtaining or improving erection; and

- c) A chronic use to prevent or minimize penile atrophy after prostatectomy.

5        Although the present invention has been described hereinabove by way of preferred embodiments thereof, these embodiments can be modified at will, within the scope of the appended claims, without departing from the spirit and nature of the subject invention.

REFERENCES

1. Stewart, J., Autonomic Regulation of Sexual Function In Clinical Autonomic Disorders, 2<sup>nd</sup> Ed., PA Low, Lipincott-Raven Publ.,  
5 Philadelphia, 1997, pp129-134.
2. Zvara, P., Brock, GB., Determining the source of impotence, Can.,  
J.Diag., 4;49-55, 1994.
- 10 3. Pollack, MH., Smoller, JW., Management of antidepressant-induced side effects, The Guilford Press Publ., NY, NY, 1996, pp 451-489.

**WHAT IS CLAIMED IS:**

1. The use of a dopaminergic agonist in the making of a medication to improve sexual function in a subject.  
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2. The use as set forth in claim 1, wherein said agonists has an effect mediated by dopamine receptors of type 2, or type 3, or both.
3. The use as set forth in claim 1, wherein said agonist is sopirinol or  
10 pramipexol.
4. The use as set forth in claim 3, wherein said agonist is pramipexol.
5. The use as set forth in claim 4, wherein pramipexol is present in said  
15 medication at a dose of 0.125 to 0.250 mg.
6. The use as set forth in any one of claims 1 to 5, wherein said agonist is combined to an effective vasodilatation, amount of an agent capable of maintaining a high nitric oxide level.  
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7. The use as set forth in claim 6, wherein said agent is sildanofil.
8. The use as set forth in claim 7, wherein sildanofil is present in  
medication at a dose of 50 to 100 mg.  
25
9. The use as set forth in any one of claims 1 to 8, wherein said sexual function is erectile function.

10. A pharmaceutical amount of a dopaminergic agonist for improving sexual function in combination with a vasodilating amount of an agent capable of maintaining a high nitric oxide level, and an acceptable pharmaceutically acceptable carrier.

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11. The composition as set forth in claim 10, wherein said agonists has an effect mediated by dopamine receptors of type 2, or type 3, or both.

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12. The composition as set forth in claim 10, wherein said agonist is sopirinol or pramipexol.

13. The composition as set forth in claim 10, wherein said agonist is pramipexol.

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14. The composition as set forth in claim 13, wherein pramipexol is present in said medication in an amount of 0.125 to 0.250 mg.

15. The composition as set forth in any one of claims 10 to 14, wherein said agent is sildanofil.

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16. The composition as set forth in claim 15, wherein sildanofil is present in said medication in an amount of 50 to 100 mg.



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(54) Title:</b> THE USE OF DOPAMINERGIC AGENTS IN THE MANAGEMENT OF SEXUAL DYSFUNCTION  <b>(57) Abstract</b>  This invention relates to a new use of dopaminergic agonists for improving sexual function, particularly erectile function. Preferred agonists are pramipexol and ropirinol which present much less side effects than agonists of previous generations. Pramipexol has been further used successfully in combination with sildenafil. A new pharmaceutical composition comprising both a vasodilating agent such as sildenafil and a dopaminergic agonist is described and claimed.		



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# INTERNATIONAL SEARCH REPORT

Intern 1al Application No  
PCT/CA 99/00977

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K31/00 A61K31/4045 A61K31/428

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ANDERSSON: "the effect of sildenafil on apomorphine-derived increase in intracavernous pression." JOURNAL OF UROLOGY, vol. 5, no. 165, 1999, pages 1707-1712, XP000866496 page 1709, column 2, line 14 - line 24 page 1711, column 2, paragraphs 2,3 ---	1,2, 6-11,15, 16
P,X	WO 98 52569 A (PODOLSKI JOSEPH S ;ZONAGEN INC (US)) 26 November 1998 (1998-11-26) page 6, line 17 -page 7, line 12 page 14, line 20 - line 24 claims 1,4,12 --- -/--	1,2,6-16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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# INTERNATIONAL SEARCH REPORT

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PCT/CA 99/00977

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 23035 A (SMITHKLINE BEECHAM PLC ;FEARS ROBIN BRADSHAW (GB)) 25 November 1993 (1993-11-25) claims 3,4,6 ---	1-3,9
X	US 4 521 421 A (FOREMAN MARK M) 4 June 1985 (1985-06-04) column 4, line 27 - line 54 column 9, line 54 - line 58 claims 1-10 ---	1
X	WO 91 16021 A (FOREMAN MARK M) 4 June 1985 (1985-06-04) abstract page 5, line 13 - line 21 claims 19,21 ---	1,2,6,10
X	WO 98 31368 A (GREEN RICHARD DAVID ;CLARKE ANTHONY (GB); SCHERER LTD R P (GB); JO) 23 July 1998 (1998-07-23) example 11 claims 1,12,13 page 9, line 35 -page 10, line 9 examples 1-7 ---	1-3,9
X	GEMALMAZ: "sildenafil enhances apomorphine-induced intra-cavernous pressure..." JOURNAL OF UROLOGY, vol. 159, no. 5, 1998, page 91 XP002127913 paragraph [0349] -----	1,2, 6-11,15, 16

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA 99/00977

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
Present claims 1-2, 6-12, 15-16 relate to compounds defined by reference to the following param
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see FURTHER INFORMATION PCT/ISA/210

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-3, 6-12, 15-16 ALL PARTIALLY

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-2, 6-12, 15-16 relate to compounds defined by reference to the following param

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-3 (all partially), 6-12 (all partially),  
15-16 (partially)

Use of ropinirol for improving sexual function and compositions thereof.

2. Claims: 3 (all partially), 4-5, 6-12 (all partially),  
13-14, 15-16 (all partially)

Use of pramipexol for improving sexual function and compositions thereof.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/CA 99/00977

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9852569 A	26-11-1998	AU 7498098 A EP 0996447 A NO 995657 A	11-12-1998 03-05-2000 18-01-2000
WO 9323035 A	25-11-1993	AU 4312593 A EP 0641202 A JP 7506823 T	13-12-1993 08-03-1995 27-07-1995
US 4521421 A	04-06-1985	AT 63552 T AU 569539 B AU 3228084 A AU 585473 B AU 8216887 A DE 3484583 D DK 169622 B DK 169970 B DK 169948 B DK 400984 A,B, EP 0139393 A ES 535382 D ES 8602759 A FI 843282 A,B, FI 882658 A,B, GB 2146985 A,B GR 80201 A HK 98789 A IE 57848 B IL 72730 A JP 1819918 C JP 5028236 B JP 60072891 A JP 1151581 A JP 1823286 C JP 5029398 B KR 8801454 B NZ 209295 A PH 20062 A PT 79112 A,B RO 89126 A SG 46389 G ZA 8406467 A	15-06-1991 04-02-1988 04-04-1985 15-06-1989 31-03-1988 20-06-1991 27-12-1994 18-04-1995 10-04-1995 27-03-1985 02-05-1985 01-12-1985 16-03-1986 27-03-1985 06-06-1988 01-05-1985 02-01-1985 22-12-1989 21-04-1993 30-10-1987 27-01-1994 23-04-1993 24-04-1985 14-06-1989 10-02-1994 30-04-1993 10-08-1988 29-05-1987 18-09-1986 01-09-1984 30-04-1986 22-12-1989 26-03-1986
WO 9116021 A	31-10-1991	AT 173603 T AU 655420 B AU 7856391 A CA 2040914 A DE 69130529 D DE 69130529 T EP 0526566 A ES 2124225 T FI 924817 A KR 169950 B NO 300083 B NZ 237899 A NZ 270871 A PT 97441 A,B US 5474535 A US 5242391 A	15-12-1998 22-12-1994 11-11-1991 26-10-1991 07-01-1999 02-06-1999 10-02-1993 01-02-1999 23-10-1992 15-01-1999 07-04-1997 24-03-1997 28-05-1999 29-05-1992 12-12-1995 07-09-1993

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/00977

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9116021 A		US 5773020 A ZA 9102984 A	30-06-1998 29-01-1992
WO 9831368 A	23-07-1998	AU 717337 B AU 5671098 A EP 0954314 A NO 993520 A PL 334656 A	23-03-2000 07-08-1998 10-11-1999 16-09-1999 13-03-2000